cells by evaluating the relationship of the most common complications such as relapse, GVHD and infections.

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### Vaccine Responses Following Unrelated Double Cord Blood Transplantation (CBT)

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**Background:** CBT recipients may respond to post-transplant vaccines differently than other transplant groups due to the lack of transfer of donor immunity.
**Methods:** We analyzed vaccine responses in 48 CBT recipients transplanted at our center from 2005-2010 for the treatment of hematologic malignancies with myeloablative or non-myeloablative conditioning. GHVD ppx included a calcineurin-inhibitor and MMF. All patients received double unit CB grafts and no pt received ATG. Vaccination criteria included CD4+ cell count $>$ 200 cells/ul and IgG level $>$ 500 mg/dl at $>$ 6 weeks following the last IVIG dose.
**Results:** Forty-eight of 69 (70%) eligible pts alive & disease-free @ 12 months post-HCT were vaccinated. Vaccinated patients engrafted with 6/6 (n = 2), 5/6 (n = 26), or 4/6 (n = 20) HLA-matched units. Twelve pts received rituximab (median 4 doses) as planned peri-transplant therapy for B-cell malignancies (n = 6), EBV viremia/ lymphoma (n = 3), autoimmune hemolysis (n = 1), pure red cell aplasia (n = 1), or recurrent disease (n=1). Prior to immunization, 13 patients had no acute or chronic GVHD whereas 35 had prior grade II-IV acute and/or chronic GHVD. Overall, the median time to vaccination was 16.9 months post-CBT; 18.9 months in pts who received rituximab; 15.23 months in those who did not ($P = .056$). Pre-vaccination titers obtained at a median of 1 yr demonstrated that $>$ 85% of patients lacked protection against pneumococcus, H. flu, and pertussis and $>$ 50% lacked immunity against tetanus, measles, & mumps. Sero-conversion or $>$ 3- fold rise in titer was observed in $>$ 60% of patients in response to tetanus, diphtheria, H. flu, polio and pneumococcal (PCV7 or PCV13) vaccines. Following 3 doses of rHBV vaccine, 52% pt seroconverted. Only 2/35 recipients of a single Tdap developed protective pertussis titers; 0/8 pts responded to a single protein-conjugated meningococcal vaccine. To date, 20 pts including 9 adults have received an MMR at a median of 2.3 years post-CBT. 8 pts received the live attenuated varicella vaccine. To date, seroconversion following measles, mumps, & rubella vaccine occurred in 56%, 41% & 93% of pts, respectively and 5 evaluable pts seroconverted after 1 (n=3) or 2 doses of Varivax (n = 2). Survival in vaccinated patients is 100%. No serious reactions to any vaccine occurred.
**Conclusion:** CBT recipients, including adults & those with prior GVHD or rituximab therapy, are capable of responding to tetanus, diphtheria, H. flu, polio & PCV7 or PCV13 similar to other transplant groups. The sub-optimal response to pathogens associated with outbreaks in the community (Hepatitis B, Pertussis, meningococcus, measles, mumps, varicella) highlight the need to obtain pre- & post-vaccine titers to document response, and the need to define the optimal vaccination regimen in this population.

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### Isolation, Expansion & Function of Cord Blood Natural Killer Cells

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The rate of immune reconstitution (IR) is directly correlated with the number of hematopoietic stem cells (HSC) infused and is particularly delayed in patients undergoing cord blood transplantation (CBT) secondary to the limited numbers of HSC. Thus, methods to increase the number of cord blood (CB) progenitors have the potential to accelerate IR after CBT. Natural killer (NK) cells play a crucial role in early IR after HCT because they are the first lymphocyte subset to recover after transplant. CB NK cells have been reported to have incomplete maturation and require activation for effective function. Here, we report a clinically relevant method for *ex vivo* expansion of NK cells isolated from CB without the use of a stromal layer. Our group has demonstrated that CB NK cells cultured in the presence of IL-2 and IL-15 results in a multi-log increase in the number of precursors that have a significant increase in cytotoxicity against several target cancer cell lines. After 21 days in culture, there is a 1.848 $\pm$ 0.341 log fold increase in the number of CD3-CD56+ NK cells (range, 0.420 to 3.108) ($P < .001$, N=9). After culture, we also found a significant 2.612 $\pm$ 0.310 log fold increase (range, 0.979 to 3.622) ($P < .001$, N=9) in the number of CD3+CD56+ NKT cells. Evaluation of cytotoxicity against K562 cells, a chronic myelogenous leukemia, showed there was also a significant increase in cytolytic function at days 14 (31.52 $\pm$ 8.317% target cell lysis, $P < .01$, N=8) and 21 (44.22 $\pm$ 9.866% target cell lysis, $P < .01$, N=8) in culture when compared to day of isolation; similar results were seen using Jurkat cells, an acute T-cell lymphoblastic leukemia (T-ALL). Evaluation of NK cell resistant cells lines was also tested. While we found an increase in cytotoxicity toward the myeloid lymphoid leukemia cell line (MLL), MV411, after culture, the RS411 (MLL/ALL) and HDLM2 (Hodgkin's lymphoma) cell lines remained resistant to cytolytic killing (N=3). Currently, we are investigating the NK cell population(s) responsible for the cytotoxic killing and the corresponding killer cell Ig-like receptor (KIR) ligand/adhesion molecule(s) that may be responsible for function. We hypothesize that using methods to increase the number of CB NK cells have the potential to prevent early relapse, infections and graft versus host disease, as well as facilitate engraftment when administered following CBT.

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### In Vivo Generation of Thymus-Independent T Cells in a Tissue-Engineered T Cell Development Supporting Microenvironment

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Tissue engineering approaches based on implantation of biomimetic three-dimensional (3D) tissue constructs have been used for more than a decade for *in vivo* regeneration of